SYNTHESIS OF HOMOVANILLIC ACID DERIVATIVES OF CAPSAICIN-LIKE EFFECT

By

P. HEGYES and S. FÖLDEÁK

Institute of Organic Chemistry, Attila József University, Szeged

(Received December 28, 1973)

Capsaicin analogues containing inverse acid-amide bonds, alkyl-amides of homovanillic acid, were prepared and their pungent and desenzitizing effect, as well as the relation of the latter to the structure of the compounds were investigated.

New homovanillic acid derivatives of capsaicin-like effect (esters and carboxamides) were prepared, in order to study the connections beetween pungent effect and chemical structure. The present paper deals with preparation and effects of the amides of homovanillic acid.

Pungency of natural and synthetic products, and chiefly investigation of their structural elements responsible for this effect, attracted the interest of a number of investigators. Among them, NELSON [1], NEWMANN [2], OFF and ZIMMERMAN [3], SZÉKI [4], and JANCSÓ [5] are to be mentioned, who performed pioneer work in this field. On the basis of their work, the above connections can be summarized as follows.

For producing pungency, the fellowing structural elements are necessary:

(*a*) *p*- or *o*-hydroxybenzylamine or their ring-substituted derivatives, in alkyl--acid amide bonding

(*b*) *p*-hydroxy group is more effective than *o*-hydroxy group

(*c*) substitution of the hydroxy group results in ceasing of the pungent effect

(*d*) vanillin-amide derivatives are the most pungent, but guaiacol and ethanolamine derivatives are also effective

(*e*) only aliphatic carboxamide analogues have a pungent effect

(*f*) C_9—C_{11} straight-chain carboxamides are the most pungent.

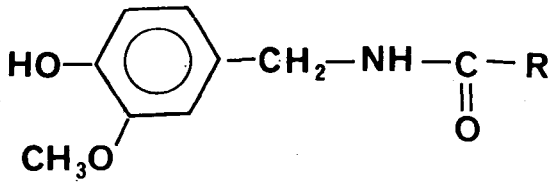
On the basis of these connections, it is chiefly vanillyl alkyl amides which (**I**) produce the pungent effect.

Continuing the research of these connections, we made use of the principle of interchangeability of the prosthetic groups (HN—CO—), and synthesized alkyl--amides of homovanillic acid (**II**) in order to study their pungency. Suprisingly, we found not only pungent species among these compounds, but also some of stronger desenzitizing effect than capsaicin.

An obvious explanation of this circumstance is the structural similarity of **I** and **II**. The change in the bonding of the acid amide in inverse position, as one of the prosthetic groups responsible for the effect, did not diminish, but rather

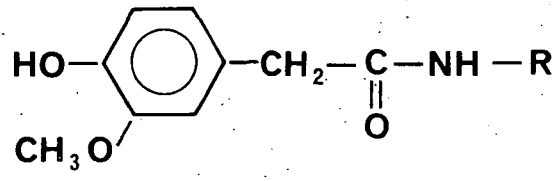
increased the effect. Concerning other effects, we had found earlier that inversion in the acid amide function did not cause loss of the effect [8].

The changes in pungency of the compounds of type **II** on changing the alkyl chain R, compared also with the capsaicin homologues, are shown by the hatched



I a-c

Fig. 1



II a-g

Fig. 2

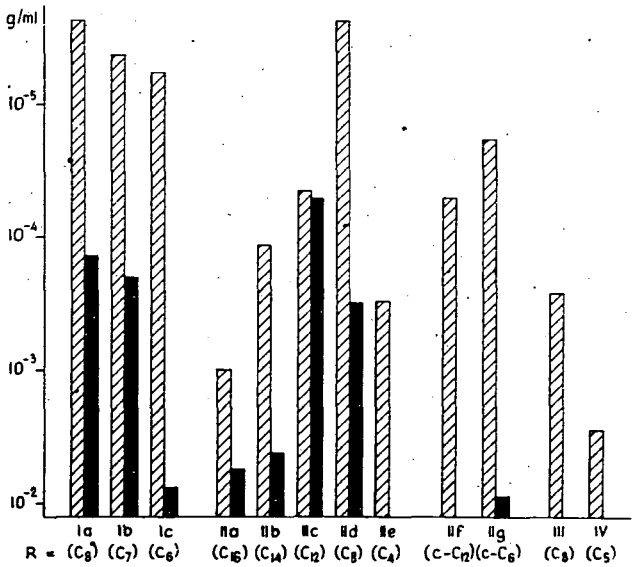


Fig. 3

columns of Fig. 3. It can be seen that the pungency first increases, then decreases with the number of C-atoms, with a maximum in the case of the C_8 amide. The connection with the desenzitizing effect (black columns) is interesting, as it does not go parallel to the pungency but reaches its maximum at C_{12}. Among the compounds of type **II** investigated, we did not find any having only desensizitizing effect (without pungency), so it is to be inferred that the structure is responsible for both effects. From the fact that cycloalkyl derivatives are only pungent and have no desensizitizing effect, it seems probable that the latter is to be attributed to the NH-groups.

Experimental

The course of the reactions was followed by thin layer chromatography; the purity of the products was controlled by m.p. measurement, elementar analysis and IR spectroscopy.

All melting points were measured on a Kofler-block; the m.p. values given are uncorrected. IR measurements were made generally in KBr pellets (in some cases in nujol) with a Unicam SP 200 IR spectrophotometer.

Homovanillic acid [6]

To 150 ml 21% sodium bisulfite solution (technical grade) 30.4 g vanillin was added (three-necked flask, mixer, reflux cooler, dropping funnel) and mixed at room temperature until the vanillin totally dissolved; then the solution was cooled to −5—10°C, and 26 g (0.4 mole) sodium cyanide dissolved in 40 ml water was slowly dropped to the cooled solution. The reaction mixture was stirred for 30 minutes after the KCN addition; during this time it transformed to a crystalline masse, which, after adding 60 ml 5*N* H_2SO_4 dropwise in an hour and continuing the stirring for another hour, was filtered.

The substance remaining on the filter was washed with ether three times. The ethereal phase was acidified with 1—2 ml glacial acetic acid and the ether destilled off. The residue is a yellowish oil, 4-hydroxy-3-methoxyamigdalic acid nitrile, wich can be used without further purification.

35 g (0.195 mole) of the acid nitrile obtained was measured into a round bottomed flask and 66 g (0.29 mole) $SnCl_2.2H_2O$ dissolved in 58.5 ml 37% HCl was added, shaken throroughly and heated on 110°C oil-bath for 3.5 hours. After the reaction had come to an end, the mixture was diluted with 25 ml water, left standing for 12 hours and filtered. The air-dried substance was recrystallized from 50 ml boiling water. M.p. 142°C, yield: 14.0 g (38.4%).

Acetylhomovanillic acid [7]

25 g homovanillic acid dissolved in 150 ml acetic anhydride was refluxed for 6 hours, then diluted with 1600 ml water. The diluted solution was stirred at room temperature for two hours, possible solid substances filtered off, and the filtrate evaporated to dryness. The midly yellowish, crystalline residue was recrystallized from boiling water (white plates). M.p. 115—137°C. Analysis: Calc.: C 58,64; H 5.30. Found: C 59.19; H 5,40%.

Acetylhomovanillic acid chloride [7]

20 g acetylhomovanillic acid was suspended in 25 ml thionyl chloride and heated on water bath for an hour. The greenish-yellow solution was evaporated to dryness, taken up in 25 ml abs. benzene and evaporated to dryness again. The latter process was repeated three times. The remaining light-yellow oil crystallizes after standing overnight and can be used with further purification.

Preparation of acetylhomovanillincarboxamides

0.01 mole acetylhomovanillic acid chloride was dissolved in 15 ml abs. benzene with ice-cooling and stirring. To the solution cooled to about 8—10°C, 0.02 mole amine dissolved in 15 ml abs. ether was added dropwise. The reaction mixture was stirred with ice-cooling for 3 hrs., then at room temperature for 1 hr. The hydrochloride precipitated was filtered, washed with 2×10 ml ether. The filtrate was extracted with water (until the water became neutral) and dried over Na_2SO_4. After removing the solvent, the remaining carboxamide was recrystallized from ethanol.

Table I

Acetylhomovanillincarboxamides

Formula	Amines used	M.w.	Calculated / Found % C	H	N	M.p. °C	Yield %	νC=O Carboxamide	νC=O Acetyl
$C_{19}H_{25}O_4N$	3-azabicyclo-(3.2.2)nonane	331.41	68.85 68.33	7.60 7.20	4.25 4.51	97—101	78	1642	1758
$C_{23}H_{37}O_4N$	dodecylamine	391.54	70.55 69.78	9.52 9.74	3.57 3.33	81—82	85	1650	1755
$C_{17}H_{23}O_4N$	homo-piperidine	305.38	66.86 66.53	7.59 8.02	4.58 4.43	oil	83	1648	1750
$C_{19}H_{29}O_4N$	dibutylamine	335.45	68.03 68.78	8.71 8.96	4.17 4.00	oil	85	1640	1755
$C_{19}H_{27}O_4N$	cyclooctyl-amine	333.43	68.44 69.11	8.76 9.02	4.20 3.96	oil	85	1652	1756
$C_{18}H_{27}NO_4$	heptylamine	321.42	67.26 66.73	8.15 8.28	4.35 4.04	oil	75	1645	1752
$C_{19}H_{19}O_6N$	piperonylamine	357.36	63.58 64.02	5.36 5.50	3.91 3.60	oil	70	1644	1755
$C_{25}H_{41}O_4N$	tetradecyl-amine	419.61	71.56 70.80	9.84 9.78	3.33 3.40	86—89	95	1650	1758
$C_{16}H_{21}O_4N$	piperidine	291.35	66.00 65.78	7.27 7.53	4.81 4.60	55—57	76	1645	1755

Preparation of homovanillincarboxamides

(*a*) 0.01 mole $KHCO_3$ was suspended in 30 ml abs. ethanol and the solution of 0.01 mole acetylhomovanillincarboxamide in 10 ml ethanol was added. The reaction mixture was stirred at room temperature for 4—10 hours, then mildly acidified with HCl. 50 ml water was added to the mixture and the precipitate extracted with 3×30 ml benzene, the benzene phase washed with water to neutrality and dried over Na_2SO_4, the benzene evaporated in vacuum and the oily residue crystallized from ethanol.

(*b*) If the amine component is used in at least threefold excess in the preparation of the acetylhomovanillincarboxamide and the acetylcarboxamide is not isolated but stirred at room temperature for 10—12 hours, quantitative hydrolysis of the acetyl groups occurs. After the stirring, isolation is performed as described under (*a*).

The physical constants of the acetylhomovanillincarboxamides and homovanillincarboxamides prepared are presented in Tables I and II.

* * *

We wish to exspress our thanks to Dr. A. GÁBOR-JANCSÓ and Dr, J. SZOLCSÁNYI for kindly performing the pharmacological investigations and to L. FÖLDHÁZI for preparing the starting materials.

Table II

Homovanillic carboxamides

Formula	Amines used	M.w.	Calculated / Found % C	H	N	M.p. °C	Yield %	ν C=O Carboxamide	ν OH Hydroxy
$C_{17}H_{23}O_3N$	3-azabicyclo-(3.2.2)	289.38	70.56 70.51	8.01 8.31	4.84 4.91	153—154	95	1600	3200
$C_{21}H_{35}O_3N$	dodecylamine	349.52	72.27 71.81	10.10 10.10	4.00 4.04	70.5—71	98	1650	3600
$C_{15}H_{21}O_3N$	homopiperidine	263.34	68.41 68.62	8.03 8.21	5.31 5.16	110—111.5	90	1610	3200
$C_{17}H_{27}O_3N$	dibutylamine	293.41	69.59 68.62	9.27 9.38	4.77 4.78	56.5—57.5	90	1630	3350
$C_{16}H_{25}O_3N$	cyclooctylamine	291.40	70.07 69.94	8.64 8.73	4.80 5.05	48—50	96	1642	3400
$C_{17}H_{25}O_3N$	heptylamine	279.38	68.78 67.78	9.01 9.58	5.01 5.70	oil	91	1650	3400
$C_{17}H_{17}O_5N$	piperonylamine	315.33	64.75 64.15	5.43 5.17	4.44 4.37	119—120.5	90	1628	3440
$C_{23}H_{38}O_3N$	tetradecylamine	378.56	72.97 73.36	10.11 10.48	3.70 3.95	75.5—76	96	1650	3600
$C_{14}H_{19}O_3N$	piperidine	249.31	67.44 67.45	7.68 7.39	5.61 5.02	oil	93	1630	3800

References

[1] *Nelson, E. K.:* J. Am. Chem. Soc. **41**, 1115 (1919); **42**, 597 (1920); **45**, 2179 (1923).
[2] *Newmann, A. A.:* Chem. Prod. London **27**, 343, 379, 413, 467 (1953); **28**, 14, 102 (1954).
[3] *Ott, E., K. Zimmermann:* Ann. **425**, 314 (1921).
[4] *Széki, T.:* Archiv der Pharm. und Ber. Dtsch. Pharmazeutische Ges. **268**, 1 (1930).
[5] *Jancsó, N.:* Pharmacology of Pain, Vol. 9, Pergamon Press, Oxford (1968).
[6] *Grewe, R., H. Fischer:* Chem. Ber. **96**, 1520 (1963).
[7] *Fischer, A. E., H. Hibbert:* J. Am. Chem. Soc. **69**, 1210 (1947).
[8] *Porszász, J., P. K. Gibiszer, T. Barankai, S. Földeák, B. Matkovics:* Separatum of II. Conferentia Hungarica pro Therapia et Investigatione in Pharmacologia (1964).

СИНТЕЗ ПРОИЗВОДНЫХ ГОМОВАНИЛИНОВОЙ КИСЛОТЫ С АНАЛОГИЧНЫМИ ПО ВЛИЯНИЮ СВОЙСТВАМИ КАПСАИЦИНА

П. Хедьеш, Ш. Фелдеак

Были синтетизированы алкиламиды гомованилиновой кислоты — аналоги капсаицина, со структурными элементами обратной связи амида карбоновой кислоты, изучены их горькие свойства и эффект десенсибилизации. Коротко излагаются выводы относительно данной химической структуры и ее влияния.